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Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS, or COVID-19: initial assessment

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Abstract

Introduction

Several antiretroviral drugs are being considered the treatment of COVID-19, the disease caused by a newly identified coronavirus, (SARS-CoV-2). We systematically reviewed the clinical outcomes of using antiretroviral drugs for the prevention and treatment of coronaviruses and planned clinical trials.

Methods

Three databases were screened from inception to 17 March 2020 for studies reporting clinical outcomes of patients with SARS, MERS, or COVID-19 treated with antiretrovirals.

Results

From an initial screen of 413 titles, 1 randomized trial and 22 observational studies provided clinical outcome data on the use of antiretroviral drugs; most studies reported outcomes using LPV/r as treatment. Of the 20 observational studies reporting treatment outcomes, there were 3 studies among patients with SARS, 6 studies among patients with MERS, and 11 studies among patients with COVID-19. In the randomized trial 99 patients with severe COVID-19 illness were randomized to receive LPV/r (400mg/100mg twice a day) and 100 patients to standard of care for 14 days: LPV/r was not associated with a statistically significant difference in time to clinical improvement, although LPV/r given within 12 days of symptoms was associated with shorter time to clinical improvement; 28 day mortality was numerically lower in the LPV/r group (14/99) compared to the control group (25/100) but this difference was not statistically significant. The certainty of the evidence for the randomized trial was low. In the observational studies 2 out of 227 patients who received LPV/r died; the certainty of evidence was very low. Two studies reported a possible protective effect of LPV/r as post-exposure prophylaxis. Again, the certainty of the evidence was very low due to uncertainty due to limited sample size.

Conclusions

On the basis of the available evidence it is uncertain whether LPV/r and other antiretrovirals improve clinical outcomes or prevent infection among patients at high risk of acquiring COVID-19.

Introduction

Several antiretroviral drugs are being considered for use in the treatment of COVID-19, the disease caused by a newly identified coronavirus, (SARS-CoV-2). Protease inhibitors have been considered as candidate therapy because they inhibit enzymes that activate envelope glycoproteins as part of the process of viral entry into cells.[1] The use of lopinavir/ritonavir (LPV/r) has been supported by data from in vitro studies, animal models, and positive clinical outcomes when LPV/r was given to patients infected with severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) diseases also caused by coronaviruses.[2-5] Other antiretrovirals have been proposed based on virtual screening and in vitro studies, and several clinical trials are planned. Lopinavir/ritonavir (LPV/r) is included in rapid guidance issued by researchers from Wuhan University based on clinical use during prior epidemics of severe acute respiratory syndrome (SARS) and MERS coronavirus (CoV) infections.[6].

This systematic review summarizes the clinical outcomes of using antiretroviral drugs for the prevention and treatment of coronaviruses and planned clinical trials.

Methods

Based on in vitro activity, molecular docking studies, or reported use in prior reviews the following drugs were screened[7-11]: lopinavir/ritonavir, emtricitabine, tenofovir, atazanavir, ritonavir, darunavir, nelfinavir, indinavir, saquinavir, lamivudine and zidovudine (Search strategy provided in Supplementary File 1).

Three databases - Medline via PubMed, EMBASE, and the Cochrane Library – were screened from inception to 18 March 2020 for studies reporting clinical outcomes of patients with SARS, MERS, or COVID-19 treated with antiretrovirals; studies using antiretrovirals for the prevention of these infections were also sought. The WHO database of publications on COVID-19 was also searched https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov.

Any study design that reported clinical outcome data was included, and there were no language restrictions. Clinicaltrials.gov was searched for ongoing and completed trials. Data are summarized per study, but not pooled in meta-analysis due to the limited number of studies reporting outcomes for each

disease. The review was conducted by a single reviewer (NF), with data extraction validated by a second reviewer (AR). The quality (or certainty) of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[12]

Results and Discussion

Antiretroviral drugs for treatment

From an initial screen of 414 titles, 1 randomized controlled trial and 19 observational studies provided clinical outcome data on the use of antiretroviral drugs. Three studies were excluded: 1 because cause of infection was unclear [13], 1 because the original study was retracted during the conduct of this systematic review [14], and 1 because lamivudine was given to control chronic hepatitis B infection and its use could not be linked to SARS outcomes [15]. Among the included studies, the majority reported outcomes using LPV/r as treatment; two 2 studies reported outcomes among HIV-positive individuals who were on a combination antiretroviral drugs for management of HIV.[16,17]

Characteristics of included studies and patient outcomes are summarized in Table 1.

1. SARS

Two observational studies and 1 case report among patients with SARS[2,17,18] reported outcomes of patients who were given antiretrovirals. A study from China reported a reduction in mortality in patients receiving LPV/r of 2.3% (95%CI 0-6.8%) compared to matched controls (15.6%, 9.8-22.8%).[2]. A second study from China reported that none of the 41 patients given LPV/r died compared with 7 of 111 patients in the control group.[18]. The third study, also from China, was a case report of a 30-year old HIV-positive man who recovered; he was receiving abacavir, efavirenz, tenofovir, and LPV/r as antiretroviral therapy.[17] All patients also received ribavirin and steroids of varying dose and duration.

2. MERS

Six observational studies, including 2 retrospective observational studies[3,19] and 4 case reports[16,20-22] – 1 was from Greece, 1 from Austria, 2 from Saudi Arabia, and 2 from the Republic of Korea – provided data on patients diagnosed with MERS. There were 42 deaths among 165 patients who were given LPV/r together with other interventions including ribavirin and pegylated interferon.

3. COVID-19

One randomized, controlled open-label study reported on the efficacy and safety of LPV/r for treating hospitalized adults with severe COVID-19.[23]. In this trial 99 patients received LPV/r (400mg/100mg twice a day; median time between symptom onset and randomization 13 days) and 100 patients received standard care for 14 days. LPV/r was not associated with a statistically significant difference in time to clinical improvement; 28 day mortality was numerically lower in the LPV/r group (14/99) compared to the control group (25/100) but this difference was not statistically significant in the intention-to-treat analysis. Accelerated clinical recovery and reduced mortality were observed in those treated within 12 days of symptom onset, but not in those treated later. Almost half of patients in the LPV/r group (46 patients, 48.4%) and control group (49 patients, 46.7%) reported one or more adverse events: gastrointestinal-related complaints including nausea, vomiting, and diarrhea were more common in lopinavir/ritonavir group. The certainty of the evidence was low due to risk of bias (investigators not blinded to the intervention, and imprecision.

In the observational studies, three case reports, [24-26] 1 case series, [27] and 7 observational studies [28-34] reported outcomes of patients with COVID-19 who received LPV/r; 8 studies were from China, 1 was from Singapore and 2 from the Republic of Korea. Among the 227 patients in the 9 studies where outcomes could be associated with receipt of LPV/r, 2 patients died. One study reported that 53 of 56 patients received LPV/r and 3 patients died; however, it was unclear how many of the patients who died had received LPV/r [31].

LPV/r is recommended by WHO as part of second-line antiretroviral therapy [35]. Among people living with HIV receiving LPV/r diarrhoea, nausea and vomiting are commonly reported side effects at start of treatment [19]. These side effects were reported by 4 out of 5 individuals who received LPV/r for the treatment of COVID-19 in Singapore, and only 1 individual completed the 14-day treatment course as a result of adverse events.[33]

The certainty of the evidence for outcomes across these 3 diseases is very low. The sample size was small and only two studies provided comparative outcomes (one using historical controls) and none used a randomized design to be able to assess the comparative effectiveness of different interventions. Timing, duration and dose of treatment varied, and in the majority of studies patients were provided with other interventions which may have contributed to the reported outcomes. GRADE Tables are provided in Supplementary File 2.

Antiretroviral drugs as post-exposure prophylaxis

Two studies reported a possible protective effect of LPV/r against coronavirus infection.[36,37] The first, a retrospective observational study from China, noted that 0 out of 19 patients hospitalized on same floor as SARS patients contracted the disease. Of the 19 patients, 11 were on differing regimens of antiretroviral therapy; none received LPV/r.[36] The second study, from South Korea, retrospectively enrolled health care workers considered at high risk of MERS infection. Of 22 health care workers given post-exposure prophylaxis (PEP) comprising ribavirin and LPV/r, none were infected; this compared to 9 of 21 health care workers not given PEP who became infected.[37] The certainty of the evidence across outcomes was again very low due to uncertainty due to limited sample size, variability in drugs provided, and lack of information regarding intensity of exposure (Supplementary File 2).

Registered clinical trials

Of 85 titles screened, 25 registered trials were identified that plan to assess the safety and efficacy of antiretrovirals – 20 assessing LPV/r (including 1 for the treatment of MERS and 1 for SARS, the rest for COVID-19), 2 ritonavir, 2 darunavir and cobicistat, and 1 tenofovir alafenamide fumarate. Estimated completion dates are from March 2020 to January 2022 (Supplementary File 3).

Conclusions

This systematic review identified 1 randomized trial and 20 observational studies provided clinical outcome data on the use of LPV/r for the treatment of COVID-19, SARS and MERS. The randomized trial showed no clinical benefit, the observational studies were inconclusive, and the certainty of the body of evidence across all important outcomes was low or very low. Based on available evidence it is uncertain whether LPV/r and other antiretrovirals improve clinical outcomes in severe symptomatic disease or prevent infection among patients at high risk of acquiring COVID-19. Any differences in potential therapeutic effect of LPV/r between SARS, MERS, and COVID-19 may partly be due to different clinical presentations; many of the patients had complicated courses including stays in intensive care units and were on multiple concurrent, unproven treatments.

Several randomized trials are planned to assess the safety and efficacy of antiretroviral drugs, including LPV/r, for the treatment of COVID-19, MERS-CoV and SARS-CoV. While the conduct of such trials is

challenging, [38] high quality evidence is needed to improve clinical and programmatic decisions to use antiretroviral drugs for current and future coronavirus outbreaks.

The procurement and use of LPV/r or other antiretroviral drugs to treat or prevent COVID-19 infection should take into consideration the need to ensure continued availability for people living with HIV who need LPV/r as part of their antiretroviral therapy. Overuse of LPV/r for corona virus in the current epidemic runs a risk of resistance developing for a drug that is currently the mainstay of treatment for people with HIV.

WHO plans to update this review at least monthly throughout 2020, and longer as needed, to update the evidence as new studies are completed.

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The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views of the organization.

Competing interests

The authors have no conflict of interest to declare.

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Authors' contributions

NF and SN conceived the review. NF undertook all reviews and extracted the data, which was verified by AR. NF, AC, SN, AR, MV, and MD interpreted the data. All authors contributed to the writing of the manuscript and approved the final version.

Table 1. Clinical studies evaluating LPV/r for MERS, SARS and Covid-19

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	ie to Sept
empirical antibiotics RBV d/c on incident	MODS;
	tal
Greece Case report day 20 diagnos	is of
adenoca	arcinoma
colon	
Meyer LPV/r Supportive intensive care nr n/a LPV/r Comple	ete clinical

2015 [21]	29-year-old woman		therapy			0/1 died	recovery
Austria	Case report						
Shalhoub		TDF/FTC 300/200 mg	Supportive intensive care	ARVs	n/a	0/1 died	Recovered
2015 [16]	51 year old man	once daily + ATV/r 300	therapy	initiated for			
		mg/100 mg) once	IFN 2a 180mcg 1/wk, RBV	ніх			
Saudi	Case report	daily	(loading dose of 2 gm,	treatment			
Arabia			followed by 600 mg orally				
			every 12 hours)				
			Treatment for CMV				
			prophylactic				
			trimethoprim/sulfamethoxa				
			zole960 mg daily				
Kim 2016	64-year-old man	LPV/r 400/100 Q12H	Ribavarin 2gm LD, 1.2g	7 days	n/a	LPV/r:	Discharged on day
[20]			TID, IFN 2alpha 180			0/1 died	13 due to clinical
L - J	Case Report		mcg/0.5mL from day 4 of			.,	improvement
Rep Korea			admission, Empirical				
Nep Koreu			therapy with				
			piperacillin/tazobactam				
			and azithromycin from Day				
			1 of admission				
Choi 2016		138 patients received	Antibiotics, haemodialysis,	Median	n/a	LPV/r:	Median interval
[3]	120 adults	antivirals among	ECMO and convalescent	time from		24/120	from symptom
		whom 120 received	sera. >80% of patients	onset of		died	onset to death
Rep Korea	Retrospective observational	LPV/r-containing	given LPV/r also received	illness to			was 14 days
	study	regimens	IFN	treatment			
				was 6 days			
Alhumaid	41 patients	41 patients received	IFN, RBV and antibiotics	nr	n/a	LPV/r	
2018* [19]		LPV/r				17/41	
	Retrospective observational					died	
Saudi	study						
Arabia							
COVID-19							<u> </u>
	199 patients	100 adult patients	Supportive care	14 days	Supportive	LPV/r	LPV/r not
Cao 2020	Randomized trial	received LPV/r			care alone	14/99	associated with a
[23]		400/100 Q12H				died	statistically
		-00/ 100 Q1211				Control	significant
China							difference in time
China						25/100	
							to clinical
			-				improvement
Wang		LPV/r 400/100 Q12H	Umifenovir (Arbidol),	6-15 days	n/a	LPV/r:	Outcome of 1
2020 [27]	4 adult patients		SFJDC			0/3 died	patient unknown
China	Case series						
							·J

1.5		10//- 400/100 01211	Oth out the other out o	10 dava	- /-	1.01/1-1	Detions to show a
Lim 2020		LPV/r 400/100 Q12H	Other treatments	10 days	n/a	LPV/r:	Patients showed
[24]	54 year old man	from day 8 of	included: Azithromycin,			0/1 died	clinical
		admission, day 10	Ceftriaxone, Levofloxacin/				improvement
Rep Korea	Case report	from onset of	Tazobactam and 1 dose of				following
		symptoms	Peramivir				initiation with
							LPV/r
Han 2020		LPV/r 400/100 daily	Methylprednisolone (40	Unclear,	n/a	LPV/r:	Patient received
[25]	47-year-old man	on day 4 of illness	mg daily), IFN alfa-2b (10	but		0/1 died	LPV/r and was
			million IU daily), ambroxol	discharged			discharged on day
China	Case report		hydrochloride (60 mg	after 10			10.
			daily) and moxifloxacin	days			
			hydrochloride (0.4 g daily				
Kim 2020		LPV/r 800/200 daily	Oxygen supplementation	Unclear but	n/a	LPV/r:	
[26]	35 year old woman			fever		0/1 died	
				persisted			
Rep Korea	Case report			for 10 days			
Young		5 patients treated	Oxygen supplementation	within	n/a	LPV/r:	4/5 patients
2020 [33]	5 adults	with LPV/r (200		1 to 3 days		0/5 died	developed
		mg/100 mg Q12H for		of			nausea, vomiting,
Singapore	Retrospective cohort	up to 14 days)		desaturatio		3/5	and/or diarrhea,
		,		n		improved	and 3 developed
						2/5	abnormal liver
						develope	function test
						d	results.
						progressi	Only 1 completed
						ve	the full 14-day
						respirato	treatment course
						ry failure	treatment course
Chen 2020		LPV/r 500 mg Q12H	oseltamivir (75 mg every	3-14 days	n/a	2/75 died	57 remained in
	99 patients, of which 75 received	LPV/1 500 INg Q12H		5-14 uays	11/ d	2/75 uleu	hospital
[28]			12 h, orally), ganciclovir				
China	LPV/r		(0.25 g every 12 h,				31 discharged
China			intravenously).				11 died
	Retrospective cohort		Antibiotics				
						1014	
Jun 2020		LPV/r Q12H for 5 days	IFN alpha-2b and		ArdiboL: 34	LPV/r:	No reported
[29]	52 patients received LPV/r		supportive care		patients	0/52	deaths
					No		
China	Retrospective cohort				antivirals:		LPV/r: 2/52
					48 patients		severe
							Abidol: 1/33
							Control: 2/48
	1						

						1	
Liu 2020	10 patients received LDV/r	LPV/r 400/100 Q12H	Owgon supplementation	E dave from	n/a	LPV/r:	
	10 patients received LPV/r	LPV/1400/100 Q12H	Oxygen supplementation.	5 days from	n/a		
[32]			I patient also received TDF	onset of		0/10	
	Retrospective cohort		for underlying liver	symptoms			
China			disease. 9/10 also received				
			IFN alpha-2b				
Deng [30]	33 patients received LPV/r	LPV/r 400/100 Q12H	Some patients received	5-21 days	16/33	LPV/r:	After 14 days,
			corticosteroids		patients	0/17	coronavirus no
China	Retrospective cohort		Supportive care		also		longer detected
					received	LPV/r/ar	by PCR
. i .					arbidol	bidol:	
						0/16	
Liu [31]	56 patients, of which 53 patients	LPV/r 400/100 Q12H	Some patients received		n/a	3/56	Outcomes not
	received LPV/r		IFH & traditional Chinese			Unclear	linked to receipt
China			medicines			Who	of LPV/r
	Retrospective cohort					received	
						LPV/r	
Cai[34]	45 patients received LPV/r	LPV/r 400/100 Q12H	IFN-α1b 60 μg twice daily	14 days	Favipiravir	0/45 died	
culloij				1 adys	Tutipituti	o, is alca	
China	Comparative cohort study						
Prevention							
Chan 2003		11/19 patients	Remaining 8 patients	15 patients	n/a	LPV/r:	All 19 HIV patients
	10 notionts Individuals with UN(11/ d		
[2]	19 patients Individuals with HIV	received ARVs:	received treatment for	stayed for		0/1	(with AIDS) on the
	(AIDS) infected with SARS	D4T/3TC/EFV =3,	opportunistic infections	>1month		infected	floor tested
China		d4T/3TC/NVP = 2,		with SARS			negative for SARS
	Retrospective cohort	d4T/ddl/NVP =3,		patients on			
		Combivir/EFV = 1,		the same			
		Indinavir/EFV =2		floor.			
Park 2019		22 received PEP and	2 HCWs in the non-PEP	PEP given	Historical	LPV/r:	6/43 had MERS-
[37]	123 HCWs with unprotected	21 were not given	group wore masks, 3	until day	controls	0/22	CoV infection;
	exposure to a MERS-CoV case of	PEP; PEP protocol was	HCWs wore gloves as	14,	from 4	infected	Attack rate in PEP
Rep Korea	which 43 had a high-risk	RBV + LPV/r initiated	personal protective	initiated	hospitals		Vs non-PEP
	exposure	between day 1 and	equipment	within 36	located far	Control:	groups: 0% Vs
		day 3 after last		post	apart	6/21	28.6%, OR: 0.405
	Retrospective case control study	unprotected exposure		exposure,		infected	(0.274-0.599)
		to the patient		median			-
				duration of			
				PEP 12 days			

* additional information provided by the authors

ATV/r, ritonavir-boosted atazanavir; ARDS, acute respiratory distress syndrome; D4t, stavudine; ECMO, extracorporeal membrane oxygenation; MODS, multiple organ dysfunction syndrome; HCWs, Healthcare workers; IFN, Interferon alpha; IU, international units; IV, intravenous; LPV/r, boosted lopinavir/ritonavir; MERS, middle-east respiratory syndrome; n/a, not applicable; nCoV, novel coronavirus; nr, not reported; NVP, nevirapine; peg-IFN, pegylated interferon; PEP, post-exposure prophylaxis; Q12H, twice daily; RBV, Ribavarin; SARS, Severe acute respiratory syndrome; TDF, tenofovir; 3TC, lamivudine.

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